
Influenza A And B: The Virus And The Disease

Influenza: A Significant Public Health Issue

- ~200,000 hospitalizations per year caused by influenza and its complications¹
- ~36,000 deaths per year¹
- Up to 34% of adults aged 18 to 64 years visit healthcare providers for treatment of influenza²
- Annual direct and indirect medical costs of ~\$3 billion and ~\$15 billion, respectively³

¹ Centers for Disease Control and Prevention. Available at: <http://www.cdc.gov/flu/keyfacts.htm>. Accessed March 10, 2006.

² Neuzil KM et al. *Infect Dis Clin North Am*. 2001;15:123-141.

³ Szucs TD. *Pharmacoeconomics*. 1999;16(suppl 1):27-32.

Influenza Virus

- Single-stranded, helically shaped RNA virus
- Family Orthomyxoviridae
- 3 types identified:
 - influenza A
 - influenza B
 - influenza C
- All 3 types occur in humans, although only influenza A and B cause epidemic disease

Centers for Disease Control and Prevention. In: Atkinson W et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 2006:233-253.

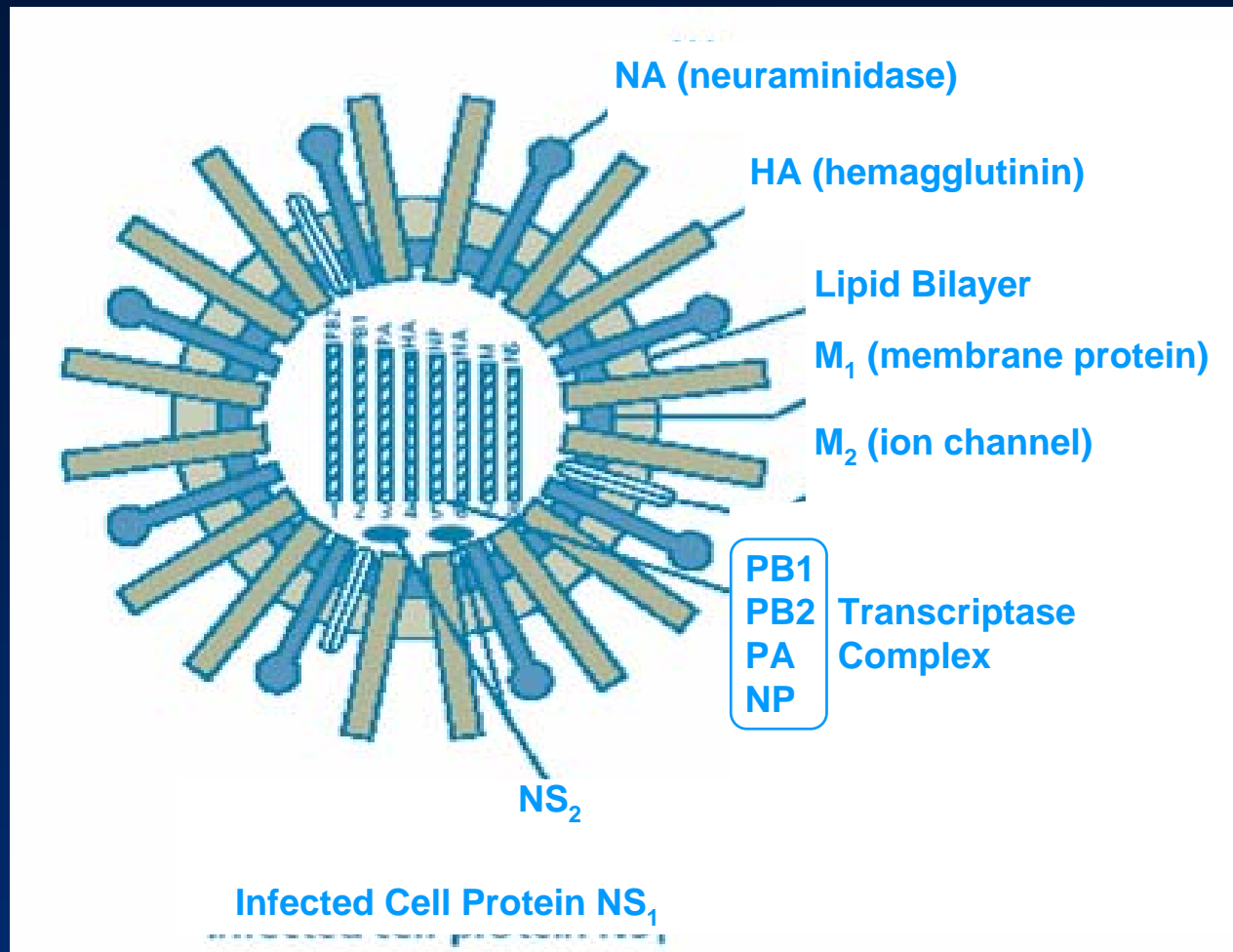
Influenza Virus Characteristics

- High infectivity¹
- Attack rates 10%-20%¹
- Subclinical infection common¹
- Genome: single-stranded RNA with 8 fragments²
- Nucleocapsid lipid envelope²
- 2 surface antigens¹
 - hemagglutinin
 - neuraminidase

¹ Mandal BK et al. *Lecture Notes on Infectious Diseases*. 1996.

² Potter CW. In: Zuckerman A et al, eds. *Principles and Practice of Clinical Virology*. 2004.

Structure Of The Influenza A Particle



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NP = nucleocapsid protein; NS = nonstructural protein; PA, PB1, PB2 = polymerase proteins.

Influenza Antigenic Changes

- Antigenic shift
 - major change, new subtype
 - caused by exchange of gene segments
 - may result in pandemic
- Antigenic drift
 - minor change, same subtype
 - caused by point mutations in gene
 - may result in epidemic

Centers for Disease Control and Prevention. In: Atkinson W et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 2006:233-253.

Viral Reassortment Theory: Antigenic Shift

- Influenza is an RNA virus
 - genome of 8 separate fragments
 - avian influenza infects mammal
 - human influenza infects same mammal
 - mammal becomes a mixing pot for fragments
- Potential to produce new virus with 8 RNA fragments
 - 6 fragments may be of human origin
 - 2 fragments may be of avian origin

Antigenic Drift

- Influenza is an RNA virus¹
- Employs RNA polymerase²
 - cannot proofread its work
- Human DNA polymerase²
 - can proofread its work
- RNA polymerase makes more errors than DNA polymerase
- Antigenic drift results from accumulation of point mutations³

¹ Mandal BK et al. *Lecture Notes on Infectious Diseases*. 1996.

² Air GM et al. *Proc Natl Acad Sci U S A*. 1990;87:3884-3888.

³ Potter CW. In: Zuckerman A et al, eds. *Principles and Practice of Clinical Virology*. 2004.

Influenza A Virus Mutations

- Antigenic drift¹
 - small continuous change¹
 - error prone RNA polymerase²
- Antigenic shift¹
 - major sudden change
 - exchange of RNA fragments in animal reservoir

¹ Mandal BK et al. *Lecture Notes on Infectious Diseases*. 1996.

² Air GM et al. *Proc Natl Acad Sci U S A*. 1990;87:3884-3888.

Influenza B Virus Characteristics

- Causes relatively few cases¹
- Local epidemics about every 2 years¹
- Especially children¹
- Influenza B mutation
 - antigenic drift²
 - error prone RNA polymerase³
 - no antigenic shift²

¹ Mandal BK et al. *Lecture Notes on Infectious Diseases*. 1996.

² Potter CW. In: Zuckerman A et al, eds. *Principles and Practice of Clinical Virology*. 2004.

³ Air GM et al. *Proc Natl Acad Sci U S A*. 1990;87:3884-3888.

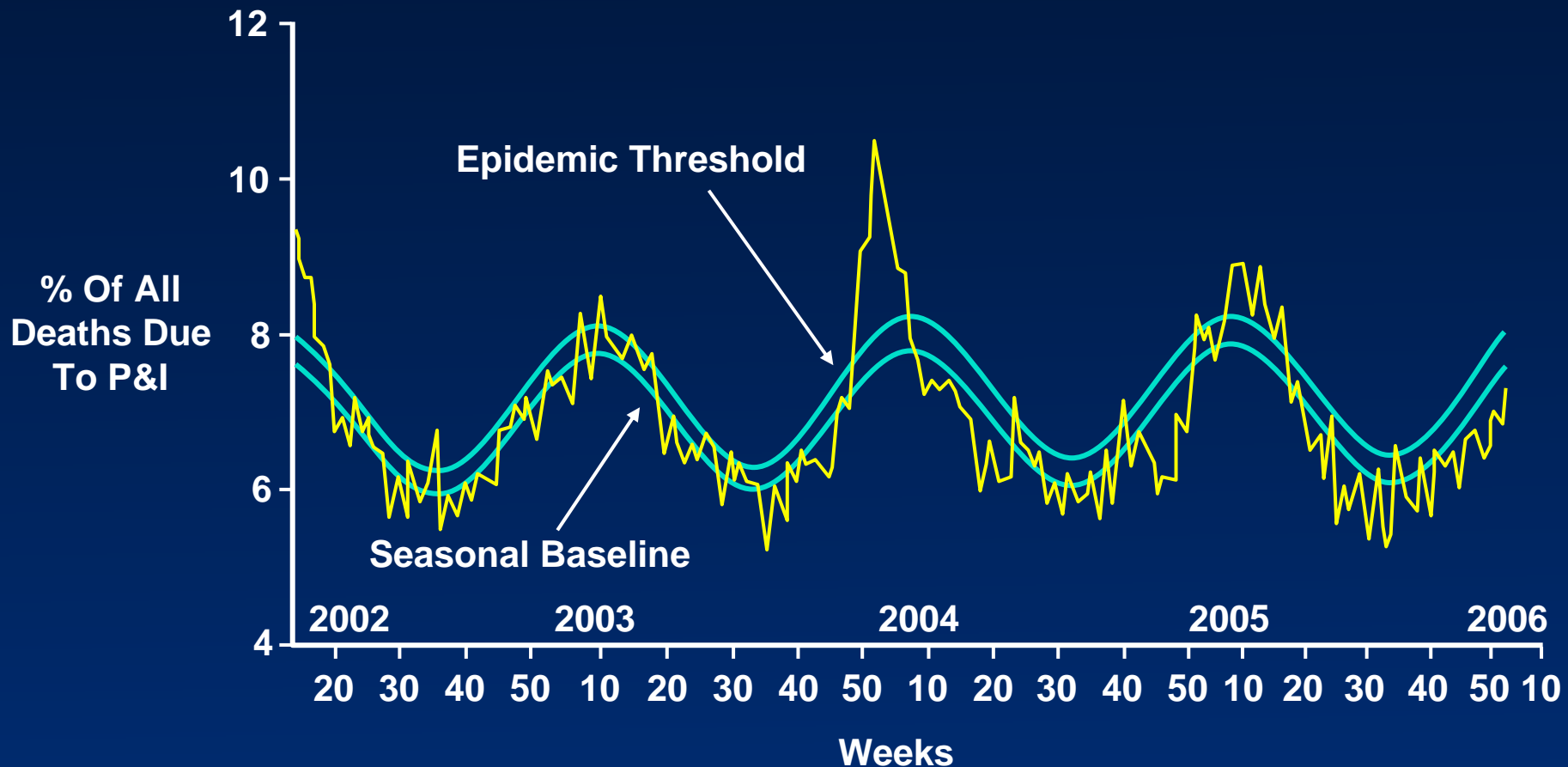
Epidemics

- Regional influenza outbreaks occur virtually every year, although duration and severity of annual epidemics may vary¹
- On average, an epidemic lasts 3 to 6 weeks in a given community¹
- Deaths resulting from influenza typically occur during the end of an epidemic²

¹ World Health Organization. *Wkly Epidemiol Rec.* 2002;77:230-239.

² Szucs TD. *Pharmacoeconomics.* 1999;16(suppl 1):27-32.

Pneumonia And Influenza Mortality In The United States, 2002-2006



Reproduced from the Centers for Disease Control and Prevention. In: Atkinson W et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 2006:233-253.

Influenza Pathogenesis

- Respiratory transmission
- Replication in respiratory epithelium with subsequent cell destruction
- Viremia rarely documented
- Virus shed in respiratory secretions for 5 to 10 days

Centers for Disease Control and Prevention. In: Atkinson W et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 2006:233-253.

Influenza Clinical Features

- Acute respiratory illness
- Abrupt onset of symptoms
 - fever/chills
 - nonproductive cough/sore throat
 - headache
 - myalgia
 - fatigue

Treanor JJ. In: Mandell GL et al, eds. *Mandell, Doulgas, and Bennett's Principles and Practice of Infectious Diseases*. 2005:2060-2081.

Influenza Systemic Symptoms

- Cytokines cause systemic symptoms
 - cytokines IL-6 and IFN- α levels correlate with systemic symptoms
 - host defenses contribute to mucosal inflammation

Hayden FG et al. *J Clin Invest.* 1998;101:643-649.

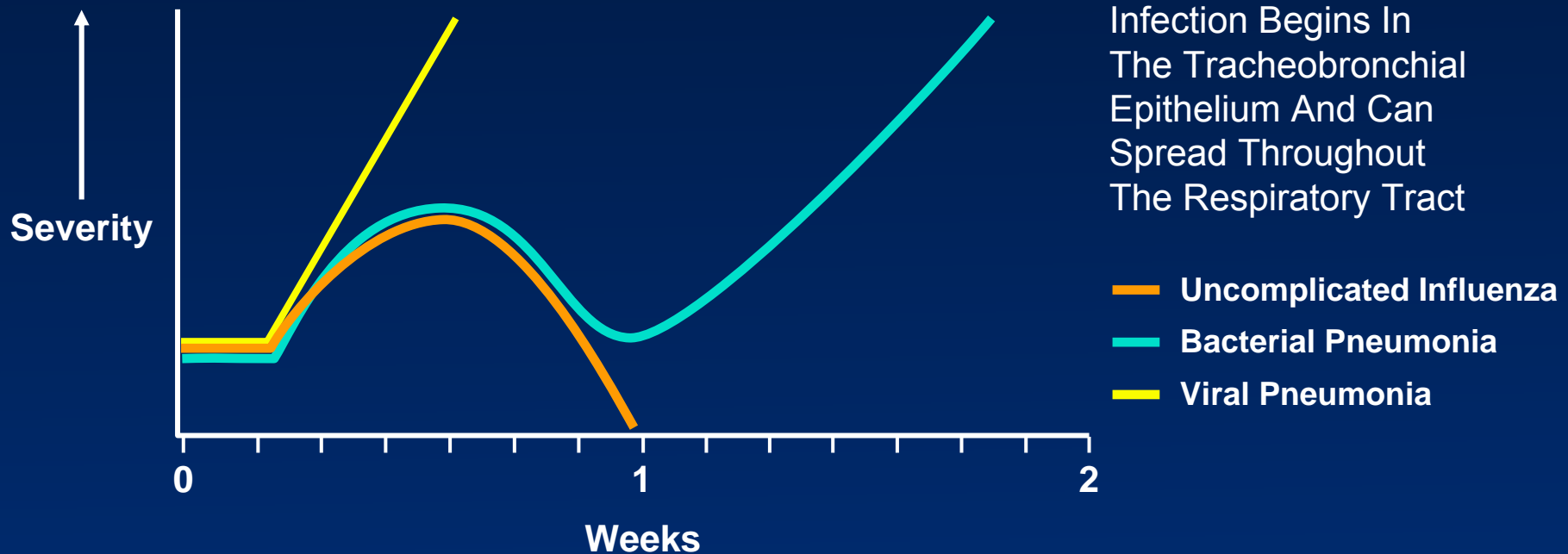
Influenza Complications

- Secondary bacterial pneumonia
 - Reye's syndrome (primarily in children)
 - Myocarditis
 - Worsening chronic bronchitis
 - Death in 0.5 to 1 per 1000 cases
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Centers for Disease Control and Prevention. In: Atkinson W et al, eds.
Epidemiology and Prevention of Vaccine-Preventable Diseases. 2006:233-253.

The Course Of Influenza In Untreated Patients

Progression Of Influenza Infection



Host Defenses Against Influenza

- Humoral antibody
- Local antibody
- Cell-mediated immunity
- Interferons
- Cytokines
- Other host defenses

Dolin R. In: Braunwald E et al, eds. *Harrison's Principles of Internal Medicine*. 2001: 1125-1130.

Cytokine Involvement

- Influenza infection is localized within the respiratory tract, but the release of cytokines is associated with systemic symptoms and host defenses
- IL-6 and IFN- α are the primary cytokines associated with influenza symptoms
- IL-6 appears to be the main cause of fever
- IFN- α induces NK cell activity
 - NK cells limit viral infection until the host mounts a primary antigen-specific B or T cell response

Hayden FG et al. *J Clin Invest.* 1998;101:643-649.

Influenza Treatment And Prophylaxis Options

- Adamantanes
 - rimantadine
 - amantadine
- Neuraminidase inhibitors
 - zanamivir
 - oseltamivir

Moscona A. *N Engl J Med.* 2005;353:1363-1373.

Adamantanes (Amantadine And Rimantadine)

- Interfere with viral uncoating inside cell
 - Effective only against influenza A
 - Associated with emergence of drug-resistant variants
 - Several possible undesirable side effects
-

Moscona A. *N Engl J Med.* 2005;353:1363-1373.

CDC Recommends Against Use Of Adamantanes For Influenza In The United States 2005-2006 Influenza Season

- Resistance of influenza A viruses to adamantanes can emerge rapidly or occur spontaneously during treatment¹
 - in the United States, resistance increased from 1.9% in the 2003-2004 season to 11% in the 2004-2005 season²
- Among 120 influenza A (H3N2) viruses tested from October 2005-January 2006, 91% were resistant to adamantanes²
- The CDC recommends that adamantanes are not used for the remainder of the 2005-2006 influenza season²
- Usefulness of the adamantanes in future seasons remains to be determined

¹ Belshe RB et al. *J Virol.* 1988;62:1508-1512.

² Centers for Disease Control and Prevention. *MMWR Morb Mortal Wkly Rep.* 2006;55:44-46.

Neuraminidase Inhibitors

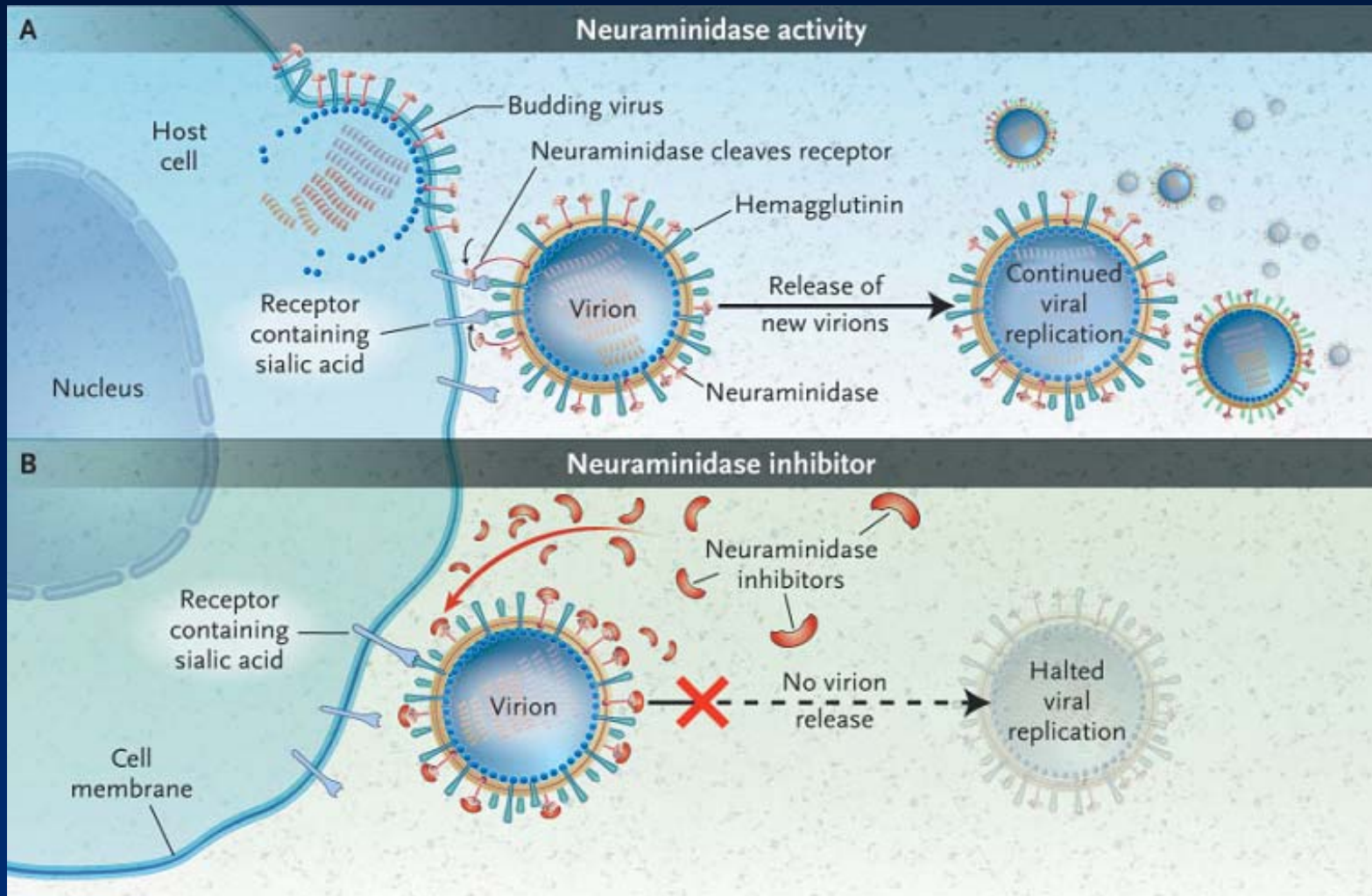
- Interfere with release of progeny influenza virus from infected host cells; prevent spread of infection in the respiratory tract
 - Effective against influenza A and B
 - Less likely to promote drug resistance
 - Little toxicity
-

Moscona A. *N Engl J Med.* 2005;353:1363-1373.

The Essential Role Of Neuraminidase

- All influenza viruses have 2 surface glycoproteins
 - hemagglutinin: mediates entry of virus into target cell
 - neuraminidase
 - ◆ cleaves sialic acid residues
 - ◆ releases virus that can infect other respiratory epithelial cells
- Without neuraminidase, infection would be limited to 1 round of replication

Neuraminidase Inhibitors: Mechanism Of Action



Reproduced from Moscona A. *N Engl J Med.* 2005;353:1363-1373, with permission.

Pandemics

- Sudden emergence of a new influenza A virus subtype and lack of immunity in the population may lead to a worldwide pandemic
- Several pandemics have occurred in the 20th century
- 1918 “Spanish flu” was the worst pandemic
 - 20 to 40 million people killed worldwide
- Future pandemics may have more devastating consequences

Centers for Disease Control and Prevention. In: Atkinson W et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 2006:233-253.

Influenza A Virus Epidemics And Pandemics

- Worldwide epidemics occur about every 1-3 years¹
- Worldwide pandemics since 1900¹
 - 1918 – H1N1 (Spanish flu)²
 - 1957 – H2N2 (Asian flu)²
 - 1968 – H3N2 (Hong Kong flu)²
- Some influenza outbreaks never reach pandemic proportions
 - 1976 – H1N1 (Swine flu scare)²
 - 1977 – H1N1 (Russian flu scare)²
 - 1997 – H5N1 (Avian flu scare)²

¹ Mandal BK et al. *Lecture Notes on Infectious Diseases*. 1996.

² US Department of Health & Human Services. Available at:
<http://www.hhs.gov/nvpo/pandemics/index.html>. Accessed April 17, 2006.

Influenza Type A Antigenic Shifts

Year	Subtype	Severity Of Pandemic
1889	H3N2	Moderate
1918	H1N1 (Spanish flu)	Severe
1957	H2N2 (Asian flu)	Severe
1968	H3N2 (Hong Kong flu)	Moderate
1977	H1N1 (Russian flu)	Mild

Reproduced from the Centers for Disease Control and Prevention. In: Atkinson W et al, eds. *Epidemiology and Prevention of Vaccine-Preventable Diseases*. 2006:233-253.

Pandemic Influenza: 1918 Morbidity And Mortality

- United States¹
 - 675,000 died
- England & Wales²
 - 200,000 died
- Worldwide
 - 500 million infected³
 - mortality
 - ♦ low: 20 million⁴
 - ♦ high: 100 million³
- Comparison mortality
 - AIDS 25 million (2005)⁵
 - The Great War⁶
 - ♦ approximately 10 million died (combat)
 - World War II⁷
 - ♦ approximately 25 million died (combat)
- Lethality/mortality³
 - 1918: 2.5% of victims
 - other pandemics: 0.1% of victims

¹ US Department of Health & Human Services. Available at: http://www.pandemicflu.gov/season_or_pandemic.html. Accessed May 26, 2006. ² Mandal BK et al. *Lecture Notes on Infectious Diseases*. 1996. ³ Taubenberger JK et al. *Emerg Infect Dis*. 2006;12:15-22.

⁴ US Department of Health & Human Services. Available at: <http://www.hhs.gov/nvpo/pandemics/index.html>. Accessed April 17, 2006.

⁵ Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO). Available at: http://www.who.int/hiv/epi-update2005_en.pdf. Accessed May 26, 2006. ⁶ Keylor WR. Microsoft Encarta Online Encyclopedia. 2006. Available at: http://encarta.msn.com/encyclopedia_761569981_13/World_War_I.html. Accessed May 26, 2006. ⁷ Ziemke EF. Microsoft Encarta Online Encyclopedia. 2006. Available at: http://encarta.msn.com/encyclopedia_761563737_15/World_War_II.html. Accessed May 26, 2006.

Avian Influenza (Bird Flu) And The H5N1 Virus

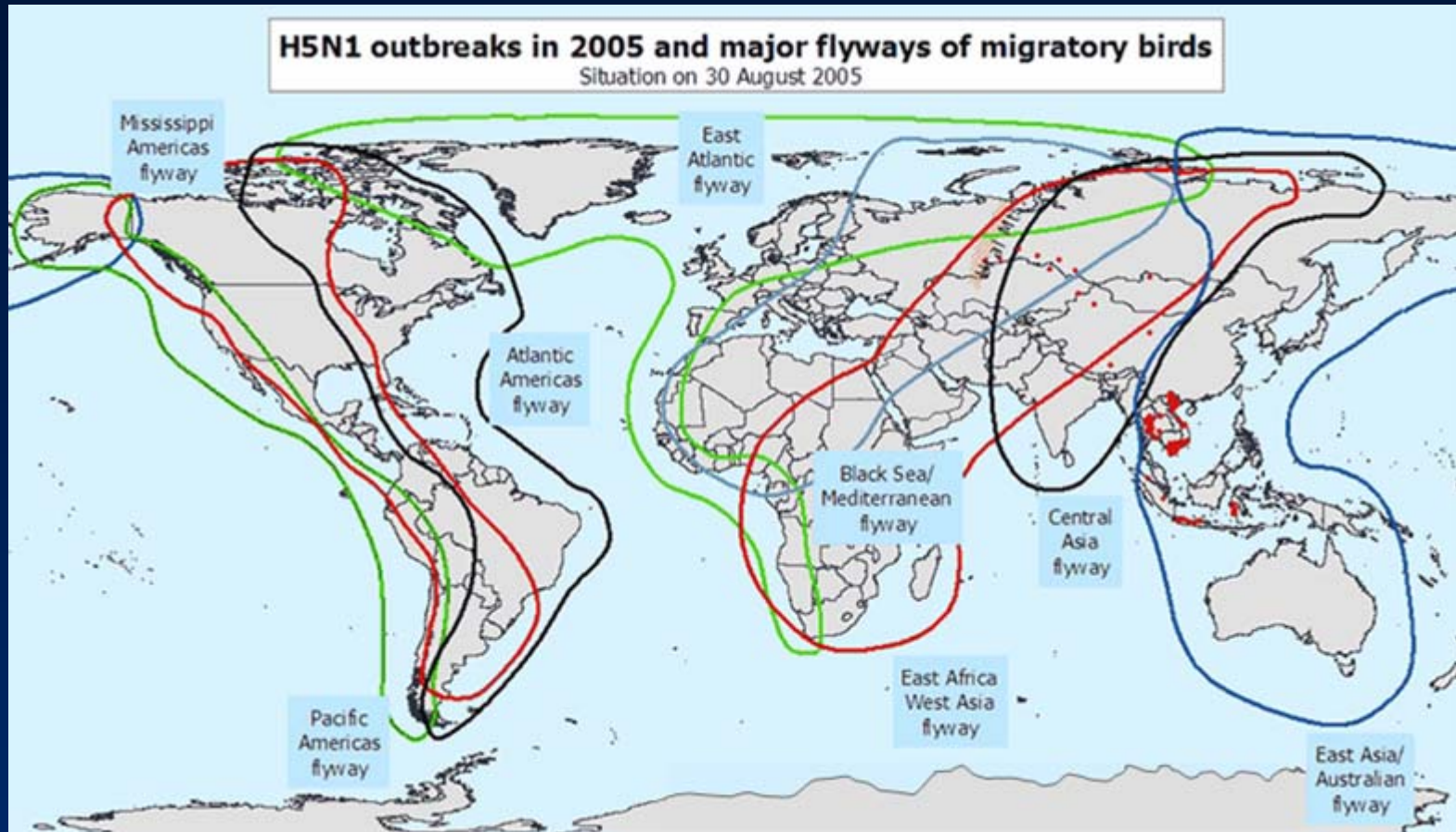
- The avian flu currently of concern is the H5N1 subtype, which is highly pathogenic
 - Many different subtypes of type A influenza viruses exist that vary based on changes in the hemagglutinin and neuraminidase proteins on the surface of the virus
 - The virus that causes avian influenza infection in domestic poultry results in a range in severity of disease
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US Department of Health & Human Services. Available at:
<http://www.pandemicflu.gov/avianbirdflu/>. Accessed February 24, 2006.

Human Infection During The H5N1 Outbreak

- H5N1 is one of the few avian influenza viruses to have crossed the species barrier to infect humans
 - human infection has mostly occurred by direct contact with diseased poultry
- H5N1 is highly pathogenic
 - in the current outbreaks in Asia and Europe, >50% of those infected with the H5N1 virus have died
- Most cases have occurred in previously healthy children and young adults

Migratory Bird Pattern



- Districts with H5N1 outbreaks since January 2005

Reproduced from United Nations Food and Agriculture Organization 2005, with permission. All rights reserved. Compiled by FAO AGAH, EMPRES Programme. Data sources: AI outbreaks: OIE, FAO and Government sources. Flyways: Wetlands International. World Health Organization. Available at: http://www.who.int/csr/disease/avian_influenza/country/cases_table_2006_03_13/en/index.html. Accessed March 13, 2006.

Pandemic Plan For The Spread Of Avian Influenza

- Because these viruses do not commonly infect humans, there is little or no immune protection against them in the human population¹
- If H5N1 virus were to gain the capacity to spread easily from person to person, a pandemic could begin¹
- The US Department of Health & Human Services (HHS) and other federal agencies are holding pandemic planning summits²

¹ US Department of Health & Human Services. Available at: <http://www.pandemicflu.gov/avianbirdflu/>. Accessed February 24, 2006.

² US Department of Health & Human Services. Available at: <http://www.pandemicflu.gov/plan/tab2.html>. Accessed February 24, 2006.

Pandemic Plan For The Spread Of Avian Influenza

US Department of Health & Human Services

- HHS Pandemic Influenza Plan
 - blueprint for pandemic influenza preparation and response
 - goal is to achieve state of readiness and quick response
 - US will work with WHO and other international partners
- Major component for preparedness includes stockpiling of antivirals and vaccines
 - production capacity to provide vaccine for entire US population
 - quantities of antiviral drugs sufficient to treat 25% of US population